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Regulatory Issues: EMA

EMA Review of Daratumumab (Darzalex) for the Treatment of Adult Patients Newly Diagnosed with Multiple Myeloma

Sotirios Michaleas,[c] Elisabeth Penninga,[d] Doris Hovgaard,[d] Anne-Marie Dalseg,[d] Aldana Rosso,[d] Sinan B. Sarac,[a,d] Jorge Camarero Jimenez,[a,e] Lucia López-Anglada Fernández,[e] Carolina Prieto Fernández,[e] Victor Mangas-SanJuan,[e,f] Isabel Garcia,[e] Concepcion Payares-Herrera,[e,g] Aranzazu Sancho-López,[g,h] Harald Enzmann,[a,i] Marcia Sofia Sanches de Castro Lopes Silva,[b,j] Sílvia Duarte,[b,j] Francesco Pignatti[c]

[a]Committee for Medicinal Products for Human Use (CHMP); [b]Pharmacovigilance Risk Assessment Committee (PRAC); [c]European Medicines Agency, Amsterdam, The Netherlands; [d]Danish Medicines Agency, Copenhagen, Denmark; [e]Agencia Española de Medicamentos y Productos Sanitarios, Madrid, Spain; [f]Interuniversity Research Institute for Molecular Recognition and Technological Development, Polytechnic University of Valencia, Valencia, Spain; [g]Instituto de Investigación Hospital Puerta de Hierro-Majadahonda, Madrid, Spain; [h]Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain; [i]Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn, Germany; [j]INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde, I.P, Lisbon, Portugal

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Daratumumab • Newly diagnosed multiple myeloma • European Medicines Agency

Abstract

The use of daratumumab in combination with established regimens for the treatment of newly diagnosed multiple myeloma has recently been authorized by the European Medicines Agency based on results from three separate phase III randomized, active controlled, open-label studies that have confirmed enhanced efficacy and tolerability in both transplant-ineligible (MMY3008 and MMY3007) and transplant-eligible (MMY3006) patients, without compromising transplant ability. Trial MMY3008 showed an improvement in progression-free survival (PFS) when daratumumab was added to lenalidomide and dexamethasone compared with lenalidomide and dexamethasone; the median PFS had not been reached in the daratumumab arm and was 31.9 months in the control arm (hazard ratio [HR], 0.56; 95% confidence interval [CI], 0.43–0.73; $p < .0001$). Trial MMY3007 showed an improvement in PFS when daratumumab was added to bortezomib, melphalan, and prednisone compared with bortezomib, melphalan, and prednisone; PFS had not been reached in the daratumumab arm and was 18.1 months in the control arm (HR, 0.5; 95% CI, 0.38–0.65; $p < .0001$). In trial MMY3006, daratumumab added to bortezomib, thalidomide, and dexamethasone was compared with bortezomib, thalidomide, and dexamethasone as induction and consolidation treatment prior to autologous stem cell transplant. The stringent complete response rate at day 100 after transplant in the daratumumab group was 29% compared with 20% in the control group (odds ratio, 1.60; 1.21–2.12 95% CI; $p = .0010$). Overall adverse events were manageable, with an increased rate of neutropenia and infections in the daratumumab arms. Regulatory assessment of efficacy and safety results from trials MMY3006, MMY3007, and MMY3008 confirmed a positive benefit-risk ratio leading to an approval of the extensions of indication. ***The Oncologist*** 2020;25:1067–1074

Implications for Practice: A set of extensions of indication was recently approved for daratumumab (Darzalex) in the setting of newly diagnosed multiple myeloma in combination with established regimens. Results of the MMY3006, MMY3007, and MMY3008 trials have shown enhanced efficacy and a favorable side effect profile of several daratumumab-based combinations in patients both ineligible and eligible for transplant, without compromising transplant ability. The combinations of daratumumab with either lenalidomide and low-dose dexamethasone or bortezomib, melphalan, and prednisone were approved for transplant-ineligible patients. The combination of daratumumab with bortezomib, thalidomide, and dexamethasone was approved for transplant-eligible patients. These combinations are expected to improve the survival outlook for patients with multiple myeloma, without an unacceptable risk of increase in

Correspondence: Sotirios Michaleas Ph.D., European Medicines Agency, Domenico Scarlattilaan 6, 1083HS Amsterdam, The Netherlands. Telephone: +31 (0)88 781 7209; e-mail: sotirios.michaleas@ema.europa.eu Received May 4, 2020; accepted for publication September 11, 2020; published Online First on October 16, 2020. http://dx.doi.org/10.1002/onco.13554

adverse events, and updated information on progression-free survival and overall survival is expected from the above trials.

Background

Multiple myeloma (MM) is a malignant disorder of the plasma cells, characterized by uncontrolled and progressive proliferation of a plasma cell clone leading to dysfunction in normal hematopoietic tissue and destruction of the normal bone marrow architecture [1, 2], resulting in progressive morbidity and eventual mortality. MM is estimated to represent 0.9% of all cancers worldwide [3] with global incidence of 160.000, prevalence of 459.000 [4], and mortality of 106.000 [3]. Incidence is increasing steadily with age with a median age at diagnosis of approximately 65 to 72 years [5–7]. According to the International Agency for Research on Cancer and the World Health Organization (2018), "The annual number of new cases of MM diagnosed is estimated to be approximately 48,297 in Europe." The estimated worldwide 5-year prevalence is approximately 230,000 patients [8]. Despite the availability of new therapies, 106,105 deaths from MM were estimated worldwide in 2018 [3], and annually, approximately 24,300 deaths are estimated in Europe [9].

In recent years, advances in understanding the molecular background of the disease have allowed the introduction and regulatory approval of novel therapeutic approaches improving patient survival. Novel treatment schemes incorporating proteasome inhibitors (bortezomib) and immunomodulatory drugs (lenalidomide or thalidomide) are competing in the role of alkylating agents in both newly diagnosed MM (NDMM) and relapsed refractory MM (RRMM) treatment [10, 11]. The standard first-line treatment for younger and fit patients with NDMM includes high-intensity induction chemotherapy, followed by autologous stem cell transplantation (ASCT) [12]. Based on response rates, depth of response, and progression-free survival (PFS), three-drug combinations including at least bortezomib and dexamethasone and any of cyclophosphamide, thalidomide, or lenalidomide are currently the standard of care before ASCT [10]. For patients who are averse to or ineligible for ASCT because of frailty, age, comorbidities, or disabilities, melphalan and prednisone combined with either thalidomide or bortezomib have been used as first-line therapeutic regimens for years [1]. Currently the standard of care has shifted toward more novel regimens [13]. Lenalidomide combined with low-dose dexamethasone is an effective therapeutic option for these patients and is an approved therapeutic option by the U.S. Food and Drug Administration and European Medicines Agency (EMA) providing significantly improved PFS and overall survival (OS) compared with the melphalan, prednisone, and thalidomide regimen [1]. Combination of bortezomib with lenalidomide and low-dose dexamethasone has been shown to further improve PFS and OS [12]. Despite advances in treatment, MM mortality remains high, with 5-year OS estimated at 52.2% [14].

Daratumumab is an IgG1κ human monoclonal antibody that binds to the CD38 protein, a surface protein that is expressed on MM cells, and inhibits the in vivo growth of CD38-expressing tumor cells. Daratumumab received a conditional marketing authorization valid through the European Union initially (May 20, 2016) as monotherapy for the treatment of adult patients with RRMM, which was subsequently (April 28, 2017) extended to include the combination with lenalidomide and dexamethasone or with bortezomib and dexamethasone as a second-line treatment [15]. More recently, promising results of daratumumab use have been reported in patients with untreated NDMM both eligible and ineligible for transplant [14], which led to regulatory submission of applications for extensions of indication in this setting. This report outlines the regulatory steps taken thereafter for the approval of the extensions of indication of daratumumab for the treatment of adult patients with NDMM (a) who are ineligible for ASCT in combination with lenalidomide and dexamethasone or with bortezomib, melphalan, and prednisone and (b) who are eligible for ASCT in combination with bortezomib, thalidomide, and dexamethasone. This article summarizes the pivotal clinical data submitted and the EMA review of the benefit-risk assessment [16–18].

Clinical Trial Designs

The regulatory approval of the extension of indication of daratumumab in the treatment of NDMM was based on three separate applications which submitted results of three phase III, randomized, active controlled, open-label studies: MMY3007, MMY3008, and MMY3006.

MMY3007 compared treatment with daratumumab in combination with bortezomib, melphalan, and prednisone (D-VMP) with treatment with bortezomib, melphalan, and prednisone (VMP) in patients with NDMM ineligible for high-dose chemotherapy with ASCT. Treatment would be continued in both arms until disease progression or unacceptable toxicity. Efficacy was evaluated by PFS based on International Myeloma Working Group (IMWG) criteria, and D-VMP was recently reported to demonstrate a survival advantage over VMP alone after approximately 40 months of follow-up [19].

MMY3008 compared treatment with daratumumab in combination with lenalidomide and low-dose dexamethasone (DRd) with treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with NDMM ineligible for high-dose chemotherapy with ASCT. Dose adjustments for lenalidomide and dexamethasone would be applied according to the manufacturer's prescribing information. Treatment would be continued in both arms until disease progression or unacceptable toxicity. Efficacy was evaluated by PFS based on IMWG criteria [20].

Study MMY3006 was a two-stage [21] randomized design study. Part 1 compared induction and consolidation treatment with daratumumab in combination with bortezomib, thalidomide, and dexamethasone (D-VTd) to treatment with bortezomib, thalidomide, and dexamethasone (VTd) in patients with NDMM eligible for ASCT. In part

Table 1. Patient population characteristics in studies MMY3007, MMY3008, and MMY3006

	Study population distribution				
Study	**Arm (*n*)**		**Age (years), %**	**ECOG performance score (%)**	**ISS stage (%)**
MMY3007	D-VMP (350)	VMP (356)	Median 71 (40–93) years 30% ≥75 years	0 (25%), 1 (50%), 2 (25%)	I (19%), II (42%), III (38%)
MMY3008	DRd (368)	Rd (369)	Median 73 (45–90 years) (≥75 years) 44%	0 (34%), 1 (49.5%), ≥2 (17%)	I (27%), II (43%), III (29%)
MMY3006	D-VTd (543)	VTd (542)	Median 58 (22–65 years) (60–65 years), 43% (50–60 years) 41% (<50 years) 16%	0 (48%), 1 (42%), 2 (10%)	I (40%), II (45%), III (15%)

Abbreviations: DRd, daratumumab with lenalidomide and low-dose dexamethasone; D-VMP, daratumumab in combination with bortezomib, melphalan, and prednisone; D-VTd, daratumumab in combination with bortezomib, thalidomide, and dexamethasone; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; Rd, lenalidomide and low-dose dexamethasone; VMP, bortezomib, melphalan, and prednisone; VTd, bortezomib, thalidomide, and dexamethasone.

2, subjects with at least a partial response by day 100 after transplant were rerandomized in a 1:1 ratio to daratumumab maintenance or observation only. Efficacy was evaluated by the stringent complete response (sCR) rate at day 100 after transplant and PFS. Only results from part 1 are described henceforth [22].

Results

Patient population characteristics in studies MMY3007, MMY3008, and MMY3006 are summarized in Table 1 illustrating distribution per study arm, age, Eastern Cooperative Oncology Group (ECOG) performance score, and disease staging based on the International Staging System (ISS).

Clinical Efficacy

For studies MMY3007 and MMY3008, efficacy was evaluated by PFS based on IMWG criteria. For MMY3007, the primary analysis of PFS showed an improvement in the D-VMP arm compared with the VMP arm; the median PFS had not been reached in the D-VMP arm and was 18.1 months in the VMP arm (hazard ratio [HR], 0.5; 95% confidence interval [CI], 0.38–0.65; $p < .0001$), representing 50% reduction in the "instantaneous" risk (hazard) of disease progression or death in patients treated with D-VMP compared with VMP alone. This figure should be interpreted with caution because the hazard is not related to the cumulative risk of progression after a certain amount of time and it does not provide direct information about the chance of obtaining a durable benefit [23]. Results of an updated PFS analysis approximately 4 months after the original clinical cutoff continued to show an improvement in PFS for patients in the D-VMP arm compared with the VMP arm (Fig. 1). Median PFS was not reached in the D-VMP arm and was 19.3 months in the VMP arm (HR, 0.46; 95% CI, 0.36–0.60; $p < .0001$). In responders, the median time to response was 0.79 months (range, 0.4–15.5 months) in the D-VMP group and 0.82 months (range, 0.7–12.6 months) in the VMP group. The median duration of response had not been reached in the D-VMP group and was 21.3 months (range, 18.4, not estimable) in the VMP group. The superiority of the daratumumab combination was maintained in patients who were aged ≥75 years and had higher ISS stage, poor performance status, and impaired hepatic or renal function.

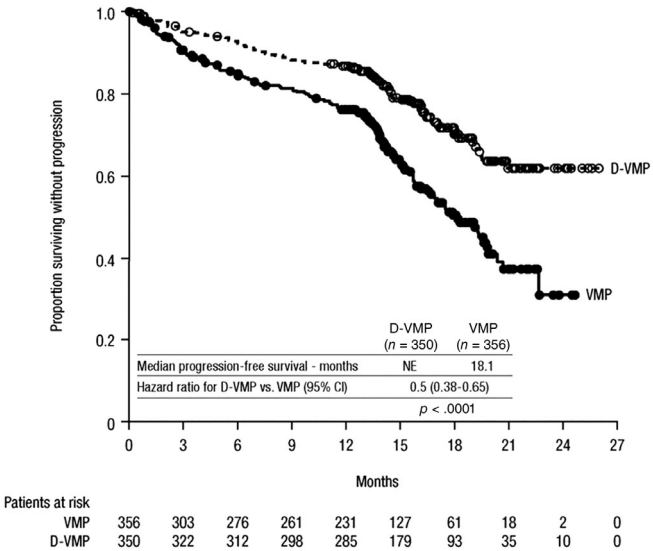

Figure 1. Kaplan-Meier curve of primary analysis of progression-free survival in study MMY3007.
Abbreviations: CI, confidence interval; D-VMP, daratumumab in combination with bortezomib, melphalan, and prednisone; NE, not estimable; VMP, bortezomib, melphalan, and prednisone.

However, patients with high-risk cytogenetics (53 patients) appeared to have less benefit compared with patients with standard-risk cytogenetics (261 patients) (HR, 0.78; 95% CI, 0.43–1.43 vs. HR, 0.39; 95% CI, 0.28–0.55, respectively). The minimal residual disease (MRD) rate was increased significantly in the D-VMP group (22.3% vs. 6.2%, $p < .001$). The overall response, very good partial response (VGPR), complete response (CR), and sCR rates were all significantly higher in the daratumumab group, as summarized in Table 2.

Study MMY3008 showed an improvement in PFS in the DRd arm compared with the Rd arm; the median PFS had not been reached in the DRd arm and was 31.9 months in the Rd arm (HR, 0.56; 95% CI, 0.43–0.73; $p < .0001$), representing 44% reduction in the instantaneous risk (hazard) of disease progression or death in patients treated with DRd compared with the Rd arm. Results of an updated PFS analysis approximately 9 months after the original clinical cutoff continued to show an improvement in PFS for patients in the DRd arm compared with the Rd arm. Median PFS was not reached in the DRd arm and was 33.8 months in the Rd arm

Table 2. Additional efficacy results from studies MMY3008, MMY3007, and MMY3006[a]

Result	MMY3008		MMY3007		MMY3006[a]	
	DRd (*n* = 368), *n* (%)	Rd (*n* = 369), *n* (%)	D-VMP (*n* = 350), *n* (%)	VMP (*n* = 356), *n* (%)	D-VTd (*n* = 543), *n* (%)	VTd (*n* = 542), *n* (%)
PFS (ITT)	HR, 0.56; 95% CI, 0.44–0.71; $p < .00001$		HR, 0.50; 95% CI, 0.38–0.65; $p < .0001$		HR, 0.50[b]; 95% CI, 0.34–0.75; $p = .0005$	
Overall response (sCR + CR + VGPR + PR)[a]	342 (92.9)	300 (81.3)	318 (90.9)	263 (73.9)	503 (92.6)	487 (89.9)
p value[c]	<.0001		<.0001			
sCR	112 (30.4)	46 (12.5)	63 (18.0)	25 (7.0)	157 (28.9)	110 (20.3)
CR	63 (17.1)	46 (12.5)	86 (24.6)	62 (17.4)	54 (9.9)	31 (5.7)
VGPR	117 (31.8)	104 (28.2)	100 (28.6)	90 (25.3)	242 (44.6)	282 (52)
PR	50 (13.6)	104 (28.2)	69 (19.7)	86 (24.2)	50(9.2)	64 (11.8)
CR or better (sCR + CR)	175 (47.6)	92 (24.9)	149 (42.6)	87 (24.4)	211 (38.9)	141 (26.0)
p value[c]	<.0001					
VGPR or better (sCR + CR + VGPR)	292 (79.3)	196 (53.1)	249(71.1)	177(49.7)	453 (83.4)	423 (78.0)
p value[c]	<.0001					
MRD negativity rate[a,d]	89 (24.2)	27 (7.3)	78 (22.3)	22 (6.2)	346 (63.7)	236 (43.5)
95% CI (%)	(19.9–28.9)	(4.9–10.5)	(18.0–27.0)	(3.9–9.2)	(59.5–67.8)	(39.3–47.8)
Odds ratio (95% CI)[e]	4.04 (2.55–6.39)		4.36 (2.64–7.21)		2.27 (1.78–2.90)	
p value[f]	<.0001		<.0001			

Abbreviations: CI, confidence interval; CR, complete response; DRd, daratumumab with lenalidomide and low-dose dexamethasone; D-VMP, daratumumab in combination with bortezomib, melphalan, and prednisone; D-VTd, daratumumab in combination with bortezomib, thalidomide, and dexamethasone; HR, hazard ratio; ITT, intent-to-treat; MRD, minimal residual disease; PFS, progression-free survival; PR, partial response; Rd, lenalidomide and low-dose dexamethasone; sCR, stringent complete response; VGPR, very good partial response; VMP, bortezomib, melphalan, and prednisone; VTd, bortezomib, thalidomide, and dexamethasone.
[a]Based on intent-to-treat population.
[b]Censored at second randomization (cutoff May 1, 2019).
[c]*p* value from Cochran Mantel-Haenszel chi-squared test.
[d]Based on threshold of 10^{-5}.
[e]Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. An odds ratio > 1 indicates an advantage for D-VMP.
[f]*p* value from Fisher's exact test.

(HR, 0.56; 95% CI, 0.44–0.71; $p < .0001$; Fig. 2). Superiority was maintained in patients aged ≥75 years, but not in the subgroup of patients with high-risk cytogenetics (HR, 0.85; 95% CI, 0.44–1.65). In responders, the median time to response was fast and almost equal between the DRd group (1.05-month range, 0.2–12.1) and the Rd group (1.05-month range, 0.3–15.3). The median duration of response had not been reached in the DRd group and was 34.7 months (95% CI, 30.8, not estimable) in the Rd group. Patients in the DRd group experienced a higher rate of deeper responses, including at least CR (47.6% vs. 24.9%). Similarly, the rates of overall response, at least VGPR, and MRD negativity (24.2% vs. 7.3%) were all higher in the DRd group (Table 2).

Efficacy of MMY3006 was evaluated by the sCR rate at day 100 after transplant and PFS. The D-VTd group showed increased rates of sCR at 100 days after transplant; the sCR rate was 29% in the D-VTd group compared with 20% in the VTd group (odds ratio, 1.60; 1.21–2.12 95% CI; $p = .0010$). In addition, the D-VTd group achieved higher rates of at least CR, at least VGPR, and MRD negativity (63.7% vs. 43.5%, $p < .0001$), as shown in Table 2. Superiority, in terms of sCR rate, was maintained in patients aged ≥50 years and in patients with poor performance status and baseline renal or hepatic dysfunction, but not in patients with ISS stage 3 MM. Patients with high-risk cytogenetics had lower odds for achieving sCR compared with standard-risk MM (odds ratio, 0.83; 0.42–1.66 95% CI). However, both subgroups showed benefit with the daratumumab combination in terms of MRD negativity and PFS. PFS analysis by censoring patients who were randomized to daratumumab maintenance in the second randomization, at the date of the second randomization, showed an HR of 0.50 (95% CI, 0.34–0.75; $p = .0005$), which is concordant with the results reported for the primary analysis.

Safety

In study MMY3007, the rate of grade 3–4 infection was increased in the D-VMP group compared with the control group (23.1% *vs.* 14.7%, respectively). Of note, pneumonia was higher in the D-VMP group (12.4% *vs.* 4%). An increased rate of serious adverse events was noted in the D-VMP group (41.6% vs. 32.5%). In study MMY3008 the most common grade 3–4 adverse events in the DRd and Rd groups

were neutropenia (50% *vs*. 35.3%, respectively) and infections (32.1% *vs*. 23.3%, respectively). Pneumonia was the most common infection, occurring in 13.7% *versus* 7.9% of patients and leading to death in 0.5% *versus* 0.8% of patients in the DRd and Rd groups, respectively. In study MMY3006 the overall incidence of serious adverse events was comparable in both groups (47% in both). There was a higher rate of grade 3–4 cytopenias in the D-VTd group (33% vs. 21.9%). Although infection rate was higher in the D-VTd group (65.5% vs. 56.9%), the rate of grade 3–4 infection was similar in both groups. Results are summarized in Table 3.

In a pooled safety data set of 2,066 patients, the most commonly reported severe (grade 3 or 4) adverse reactions were neutropenia in 39% and pneumonia in 10% of patients. The pooled safety data set includes 1,246 patients from all three studies plus 526 patients from previously assessed studies MMY3003 and MMY3004 [15], as well as five nonrandomized, clinical studies in which subjects received daratumumab either in combination with pomalidomide and dexamethasone (DPd, *n* = 103) or lenalidomide and dexamethasone (DRd, *n* = 35) or daratumumab as monotherapy (*n* = 156) [16]. In the active controlled studies, discontinuations from treatment because of infections (1%–4%) and fatal infections were generally infrequent and balanced between the daratumumab-containing regimens and the active control arms. Fatal infections were primarily due to pneumonia and sepsis. Overall, the adverse events in all studies were considered manageable and in line with the known adverse events already included in the product information of the products.

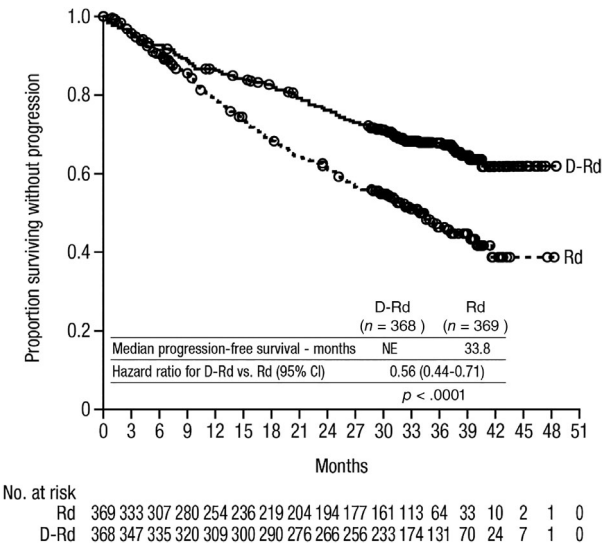

Figure 2. Kaplan-Meier curve of progression-free survival in study MMY3008.
Abbreviations: CI, confidence interval; D-Rd, daratumumab with lenalidomide and low-dose dexamethasone; NE, not estimable; Rd, lenalidomide and low-dose dexamethasone.

Assessment of Efficacy and Safety

During the assessment of studies MMY3007 and MMY3008, concerns related to the generalizability of the efficacy and safety results to the target population in clinical practice were raised because of recent changes in the management of this patient population regarding the eligibility for high-dose chemotherapy and ASCT [12]. In particular, comorbidity and physiological age have become more important factors when considering patient eligibility for high-dose chemotherapy and ASCT, a practice not encompassed by the scientific advice previously given by the Committee for Medicinal Products for Human Use. Therefore, to confirm that a similar benefit can be expected in the target population in clinical practice, which will likely be older and less fit than the one in the study, the marketing authorization holder (MAH) was requested to present separate efficacy and safety analyses for the subset of patients fulfilling any of the less controversial criteria for considering a patient who is not a candidate for stem cell transplantation such as, for example, an age ≥70 years, presence of comorbid conditions, or subjects considered unfit to undergo ASCT (e.g., as defined by the presence of an ECOG performance status of 2). In study MMY3007, a subgroup analysis was performed on patients aged at least 70 years, aged 65–69 years with ECOG performance score of 2, or aged less than 65 years with significant comorbidity or ECOG performance score of 2 (D-VMP: *n* = 273; VMP: *n* = 270). The efficacy results in this subgroup were consistent with the

Table 3. Listing of identified unfavorable effects based on safety summaries[a]

	MMY3008		MMY3007		MMY3006[b]	
Effect	**DRd (*n* = 364), %**	**Rd (*n* = 365), %**	**D-VMP (*n* = 346), %**	**VMP (*n* = 354), %**	**D-VTd (*n* = 536), %**	**VTd (*n* = 538), %**
Grade 3 or 4 AEs	89.8	82.5			80.6	75.8
SAEs			41.6	32.5		
Neutropenia	50.0	35.3			33	21.9
Infections	32.1	23.3	23.1	14.7		
Pneumonia	13.7	7.9	12.4	4		

Abbreviations: AE, adverse event; DRd, daratumumab with lenalidomide and low-dose dexamethasone; D-VMP, daratumumab in combination with bortezomib, melphalan, and prednisone; D-VTd, daratumumab in combination with bortezomib, thalidomide, and dexamethasone; Rd, lenalidomide and low-dose dexamethasone; SAE, serious adverse event; VMP, bortezomib, melphalan, and prednisone; VTd, bortezomib, thalidomide, and dexamethasone.
[a]Percentages are calculated with the number of subjects in each phase/group as denominator.
[b]During the transplant period according to protocol only limited AEs were collected.

overall population. In this subgroup, median PFS was not reached in the D-VMP group and was 17.9 months in the VMP group (HR, 0.56; 95% CI, 0.42–0.75; $p < .0001$). The overall response rate was 90% in the D-VMP group and 74% in the VMP group (VGPR rate:29% in D-VMP group and 26% in VMP group; CR: 22% in D-VMP group and 18% in VMP group; sCR rate: 20% in D-VMP group and 7% in VMP group). The safety results of this subgroup were consistent with the overall population. Furthermore, safety analysis of the subgroup of patients with an ECOG performance score of 2 (D-VMP: $n = 89$; VMP: $n = 84$) was also consistent with the overall population. Results of these analyses were also reflected in section 5.1 of the Summary of Product Characteristics. A similar approach for MMY3008 with a subgroup analysis of subjects aged 65–69, 70–75, and ≥75 years showed consistency with the intent-to-treat analysis favoring the DRd group. The presented sensitivity analyses confirmed that a similar benefit can be expected in the target population in clinical practice per current treatment guidelines. Although a more detailed analysis of the population aged >75 years would have been appreciated, being the major candidate to receive this treatment, it was recognized that its representation in the sample was adequate and that the current data appeared to be favorable for this group, which is considered the largest beneficiary of this treatment in real practice.

Regarding study MMY3006, the two-part study design and its implications in the control of multiplicity and type I error were extensively discussed during the assessment. The immaturity of the PFS data submitted and the selection of sCR by end of consolidation therapy as the primary endpoint made the assessment even more complex. The MAH has updated the results as of clinical cutoff of May 1, 2019, adding 10 months to the follow-up period with a median of 29.2 months of follow-up. The updated data were consistent with the primary analyses, by the means of sCR, CR or better, PFS, MRD negativity, and time to progression. Clarifications were also provided by the company in terms of study success criteria, dependencies between the two parts of the study, and multiplicity control.

It was highlighted that the effect of maintenance treatment received in part 2 on the favorable effects observed could not be isolated because of the study design. Because the surrogacy of sCR for PFS is not established, PFS results relevant to the effect of induction/consolidation treatment in the absence of maintenance therapy were requested in order to assess the benefit of the new regimen, given that the PFS events may also occur in the maintenance phase. The MAH presented an additional analysis for PFS in which patients who received maintenance therapy at the second randomization were censored. The results (HR, 0.50; 95% CI, 0.34–0.75; $p = .0005$) were in line with those presented in the primary analysis (HR, 0.47; 95% CI, 0.33–0.67; $p < .0001$). This additional analysis limits the contribution of daratumumab maintenance on PFS. Part of the contribution of induction effect is also removed because patients are censored at the start of maintenance therapy. Finally, the MAH committed to provide postapproval updated PFS results (including the analysis censoring patients in each arm who were randomized to daratumumab maintenance in the second randomization) in addition to the already requested OS follow-up data for the induction/consolidation patients moving on toward observation based on the planned interim analysis.

It was discussed that the depth of response in MM, as expressed by sCR or MRD, is an important prognostic factor; however, its use in the regulatory setting for clinical decision making is still debated [24]. Using the approach of testing MRD in patients with CR only, 33.7% of patients in the D-VTd group were MRD negative and in CR or better compared with 19.9% in the VTd group (odds ratio, 2.06; 95% CI, 1.56–2.72). The MAH has analyzed why MRD-negative subjects did not meet CR or sCR according to the IMWG criteria after consolidation. The main reason for not having CR/sCR was that a negative immunofixation on the serum or urine could not be established, either because of missing confirmation of the clearance of paraprotein from serum/urine or because of remaining traces of the paraprotein, so that further sampling error in patients not in CR could not be ruled out. It is acknowledged that clinical trials in MM include measurements of MRD, and future studies can hopefully clarify how MRD may be used in clinical practice.

The MAH was requested to provide an evaluation of treatment-emergent pancreatitis reported in daratumumab clinical trials. The analysis showed that in randomized trials with nondaratumumab control arms, the frequency of treatment-emergent pancreatitis was 0.9% (16/1772) in daratumumab-treated subjects compared with 0.3% (5/1775) in the nondaratumumab comparator arms (odds ratio, 3.21; 95% CI, 1.17–8.79). The overall frequency of treatment-emergent pancreatitis in daratumumab clinical trials is 0.6% (17/2935). It was concluded that the totality of the data supports the addition of pancreatitis as an adverse reaction in product information.

Interestingly, in study MMY3006, the addition of daratumumab was associated with a lower yield of stem cells compared with VTd alone (median collected CD34+ cells, 6.3×10^6/kg vs. 8.9×10^6/kg) and increased rate of plerixafor use during mobilization. However, the rates of transplant and hematopoietic reconstitution were similar. Furthermore, a recent single institution experience of 12 patients with myeloma treated with daratumumab-containing induction regimens prior to ASCT [25] reported that daratumumab leads to delayed engraftment after transplant (+3 day for neutrophiles, +1 day for platelets) compared with 129 cases with induction regimens not including daratumumab. This finding could imply that clinical trials studying daratumumab prior to stem cell transplant should report transplant-related outcomes, including feasibility of stem cell mobilization and engraftment times. Preclinical studies to identify whether daratumumab activity has a direct role in suppression of stem cell lines by daratumumab might also be required. A recent in vitro study [21] showed that daratumumab is not toxic to mobilized CD34 + progenitor cells from patients with myeloma; however, claims are limited, as not all mechanisms of daratumumab activity were extensively examined and the number of observations was small.

The risk management plan of the product has been updated after the assessment of the clinical studies [26].

The identified important risks include the possible interference for blood typing (positive indirect Coombs' test) and the possibility for hepatitis B virus reactivation. Immunogenicity has been identified as a potential risk, and the MAH has agreed on an approach to introduce a new immunogenicity assay to overcome drug interference in the detection of total antidaratumumab antibodies (ADAs; free ADAs and drug-bound ADAs) in patient serum samples with a detection limit of 100 ng/mL of positive control ADAs in up to approximately 4,000 μg/mL of daratumumab concentration. The MAH has also committed to retrospectively analyze samples from previous clinical trials using the new method. The use of daratumumab in pregnancy and lactation and the reproductive and developmental toxicity profile of the drug are currently listed as missing safety information.

Discussion

Both studies MMY3007 and MMY3008 demonstrated the added value of daratumumab addition in combination with VMP or Rd showing clinically relevant improvements in terms of PFS and response rates in patients newly diagnosed with MM who are ineligible for ASCT. These results are highly relevant in this population with a dismal prognosis. The results from secondary endpoints and subgroup analyses are all consistent with the primary endpoints. The differences in MRD negativity rates suggest a deep and more sustainable response of the daratumumab arms.

In study MMY3006, daratumumab in combination with a standard induction regime VTd resulted in deeper responses at day 100 after ASCT, in terms of sCR, MRD negativity, and achieving CR or better, in the frontline setting for patients eligible for ASCT. This higher proportion of patients achieving deeper responses after transplant is of high clinical relevance. The effect on secondary endpoints PFS and OS appeared favorable, despite relatively immature data that need to be updated after approval.

Favorable effects with the addition of daratumumab come at the cost of an increased risk of serious adverse events. In all studies, the majority of patients experienced at least one any-grade adverse event. The incidence of adverse events in the daratumumab arm was generally increased. Neutropenia; respiratory infections, particularly pneumonia; nausea; thrombocytopenia; lymphopenia; cough; hypertension; and dyspnea were the most frequent ones. Most events were clinically manageable with supportive therapy and thereby avoided discontinuation from study treatment. Overall, the addition of daratumumab to VMP, Rd, or VTd is well tolerated. The observed safety profile is as expected and in line with the safety profile of the used regimens. The discontinuation rate was low, reflecting the fact that adverse events were overall manageable in the clinical setting with supportive therapy and dose modification.

The most common side effect associated with daratumumab is infusion-related reactions (IRRs), which are experienced by approximately half of subjects receiving daratumumab IV–based regimens, with most (>90%) IRRs occurring during the first infusion. To minimize the risk of IRRs, the IV infusion requires a large infusion volume (500 to 1,000 mL) over a long period (7 hours) for the first infusion and subsequent infusions of 3 to 4 hours. Recently a subcutaneous formulation given as a flat dose (1,800 mg) was shown to be noninferior to daratumumab IV in terms of overall response rate with a lower incidence of IRR, requiring considerably shorter infusion times [27].

The most important uncertainty in all three studies remains the immaturity of OS and PFS data. Median PFS for the daratumumab arm was not reached in any of the trials. The MAH has committed to provide updated study results after authorization.

Conclusion

The overall benefit-risk ratio of daratumumab in combination with bortezomib, melphalan, and prednisone or lenalidomide and dexamethasone for the treatment of adult patients with NDMM who are ineligible for ASCT as well as in combination with bortezomib, thalidomide, and dexamethasone for the treatment of adult patients with NDMM who are eligible for ASCT is currently positive.

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Author Contributions

Conception/design: Sotirios Michaleas
Collection and/or assembly of data: Sotirios Michaleas
Data analysis and interpretation: Sinan B. Sarac, Jorge Camarero Jimenez
Manuscript writing: Sotirios Michaleas
Final approval of manuscript: Sotirios Michaleas, Elisabeth Penninga, Doris Hovgaard, Anne-Marie Dalseg, Aldana Rosso, Sinan B. Sarac, Jorge Camarero Jimenez, Lucia López-Anglada Fernández, Carolina Prieto Fernández, Victor Mangas-SanJuan, Isabel Garcia, Concepcion Payares-Herrera, Aranzazu Sancho-López, Harald Enzmann, Marcia Sofia Sanches de Castro Lopes Silva, Sílvia Duarte, Francesco Pignatti

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